REMARKS

Status of the Application

Claims 1-79 are pending in the present application.

Claims 6-8, 15-18, 21-54, 73, 74, and 76-79 have been cancelled in response to a restriction requirement, not withstanding Applicant's belief that the cancelled claims would have been allowable, and without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the cancelled (or similar) claims in another application, for the purpose of furthering Applicant's business goals and expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG).[1]

Claims 80-120 have been added to describe exemplary embodiments of the invention. In particular, support for Claims 80-86, 90-96, and 110-116 is found in the Specification[2] which discloses the recited numerical ranges for binding specificity. Support for the recitation of $\alpha V\beta 3$ integrin in Claims 81, 83, 85, 91, 93, 95, 111, 113, and 115 is also found in the Specification, on page 23, lines 6-14.

New Claim 87 which recites that the tissue is in a "human subject" is supported by the originally-filed Claim 56. The recitation in new Claims 88 and 102 of "a sarcoma, a mesothelioma, a teratocarcinoma, an astrocytoma, and a glioblastoma" is supported by the originally-filed Claim 63. Support for the recitation in new Claims 89 and 105 of "breast carcinoma, a colon carcinoma, an ovarian carcinoma and a pancreatic carcinoma" is found in originally-filed Claim 62. Support for new Claims 97-101, 103, 104, 106-109 is found in the originally-filed Claims 3-5, 9-14, 19, and 20, respectively. Newly added Claims 117-120 are supported by the recitations in Claims 13, 14, 19, and 20, respectively.

These amendments do not introduce new matter.

Applicant notes the Examiner's comments in the instant Office Action regarding Applicant's election of the claims,[3] and withdrawal of Claims 6-8, 15-18, 21-54, 73, 74, and 76-79 as being drawn to non-elected inventions.[4]

---

[1] 65 Fed. Reg. 54603 (September 8, 2000).

[2] Specification, page 23, lines 6-14.

[3] Office Action, pages 2-4.

[4] Office Action, page 2, item 1.

The Examiner required correction of a typographical error in the serial number of the priority application.[5] This has been done.

The Examiner objected to the Abstract title and suggested changing it.[6] Applicants have complied with this suggestion by changing the title "ABSTRACT OF THE INVENTION METHODS FOR DETECTING AND INHIBITING ANGIOGENESIS" to "ABSTRACT."

The Examiner further objected to the Abstract because it should be "limited to a single paragraph within the range of 50 to 250 words and should not exceed 25 lines of text."[7] Applicants have made appropriate correction.

Claims 1-5, 9-14, 19, 20, 55-72, and 75 have been rejected on the following grounds:

1. Claim 2 stands rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness;

2. Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, and 75 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.*; and

3. Claims 1-5, 9-14, 19, 20, 55-72, and 75 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* in view of Ruoslahti *et al.* and Thorpe.

Applicant believes that the present amendments and the following remarks traverse the Examiner's rejection of the claims. These remarks are presented in the same order as they appear above.

1. Rejection of Claim 2 Under 35 U.S.C. §112, Second Paragraph

Claim 2 stands rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness[8] on the ground that the term "substantially" "is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree."[9] Applicant must disagree. The Examiner is respectfully reminded that:

---

[5] Office Action, page 4, item 4.

[6] Office Action, page 5, item 5(A).

[7] Office Action, page 4, item 5(B).

[8] Office Action, page 4, item 6.

[9] Sentence bridging pages 4 and 5.

> "The precise wording of a patent claim need not be found in the patent specification as long as the claim language is clear when read in light of the disclosure of the specification as a whole."[10]

Indeed, the plain meaning of the claim's term "substantially" is clear based on the specification's teaching that:

> "a peptide that specifically binds α5β1 with at least about **two-fold** greater specificity than it binds to another integrin, for example, αvβ3, is more useful if it has at lest about a five-fold greater specificity for α5β1, and is particularly useful if it has at least about a one order of magnitude greater specificity for **α5β1** than for an integrin such as αVβ3."[11]

In other words, the specification provides a mathematical range (*i.e.*, at least about two-fold, five-fold, and ten-fold) as well as a control (*i.e.*, specificity for α5β1) to apprise the artisan of the exemplary preferred mathematical ranges for binding of the ligand to α5β1 integrin, as compared to binding of the ligand to another integrin. From this, it is clear to the artisan that the recitation of an agent which "does not substantially interfere with the specific binding of a ligand to an integrin other than α5β1 integrin" means that the agent's interference with the specific binding of α5β1 integrin to a ligand is at least **two-fold** greater than the interference of the agent with the specific binding of another integrin to its cognate ligand. In view of this, the term "substantially" is clear. Accordingly, it is respectfully requested that the rejection of Claim 2 under 35 U.S.C. §112, second paragraph, be withdrawn.[12]

Applicant notes that new Claims 86, 96, and 116 do not recite the term "substantially," which the Examiner found allegedly indefinite.

---

[10] *Oxy Metal Indus. Corp. v. Roper Corp.*, 579 F. supp. 664, 222 USPQ 33 (D. Md. 1984).

[11] Specification, page 23, lines 6-14.

[12] Applicant notes that new Claims 80-85, 90-95, nd 110-115, which recite preferred numerical ranges for binding specificity are supported by the Specification's above-referenced disclosure of numerical ranges for binding specificity.

2. **Rejection of Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, And 75 Under 35 U.S.C. §102(e) Over Pasqualini *et al.* (U.S. Patent No. 5,922,676)**

Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, and 75 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* (U.S. Patent No. 5,922,676).[13] Applicant traverses. The Examiner is respectfully reminded that:

> "Anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention."[14]

However, as discussed in more detail below, both express and inherent anticipation are absent. Furthermore, any alleged inherent anticipation is rebutted by the attached evidentiary material.

A. Express Anticipation Is Lacking

Pasqualini *et al.* discloses inhibiting tumor implantation,[15] inhibiting metastasis,[16] and regression of tumors[17] using superfibronectin (sFN). The Examiner recognized that Pasqualini *et al.* "does not specifically state that the method comprises contacting alpha 5 beta 1 integrin with an agent that interferes with specific binding of the alpha 5 beta 1 integrin to its ligand."[18] Since each of the rejected Claims 1-5, 9-13, 55-6, 68, 69, 71, 72, and 75, recites the limitation of using an "agent that interferes with specific binding of the $\alpha 5\beta 1$ integrin to a ligand," and since the Examiner conceded the **absence** of this limitation from Pasqualini *et al.*, this reference cannot expressly anticipate any of the rejected Claims 1-5, 9-13, 55-6, 68, 69, 71, 72, and 75.

With respect to rejected Claim 3 which recites that "the ligand is fibronectin," the Examiner admitted that Pasqualini *et al.* "does not specifically state that the . . . ligand is

---

[13] Office Action, page 5, item 8. The Pasqualini *et al.* patent issued on July 13, 1999 from an application filed on September 20, 1996.

[14] *RCA Corp. v. applied Digital Data Sys., Inc.*, 730 F.2d 1440, 221 USPQ 385, 388 (Fed. Cir. 1984).

[15] Pasqualini *et al.*, Example III, column 16.

[16] Pasqualini *et al.*, Example IV, column 17, and Example V, column 19.

[17] Pasqualini *et al.*, Example VII, column 21.

[18] Office Action, page 7, last full sentence.

fibronectin." The absence of this additional limitation from Pasqualini *et al.* precludes express anticipation of Claim 3.

Regarding rejected Claim 2, the Examiner admitted that Pasqualini *et al.* fails to disclose Claim 2's limitation that the "agent does not substantially interfere with the specific binding of a ligand to an integrin other than $\alpha 5\beta 1$." For this additional reason, Pasqualini *et al.* does not expressly anticipate Claim 2.

In view of the above, express anticipation is absent with respect to each and every element of the rejected claims.

B. Inherent Anticipation Is Not Established

In the absence of express anticipation, the Examiner must show that each and every element of the claimed invention is disclosed "under principles of inherency" in the cited reference.[19] Furthermore, the law is clear that:

> "In relying upon the theory of inherency, the Examiner *must* provide *a basis in fact and/or technical reasoning* to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art."[20]

The Examiner has failed to meet her burden of proof. The singular argument advanced by the Examiner in support of inherency was that "the claimed method *appears* to be the same as that of the prior art method."[21] Not a shred of evidence or reasoning was advanced in support of this position. Indeed, the Examiner engages in the type of speculation which the law finds "insufficient" to establish inherency. Because the Examiner's conclusion lacks the requisite "basis in fact and/or technical reasoning" for establishing inherency, anticipation under the doctrine of inherency cannot be established with respect to any of the rejected Claims.

In view of the admitted absence of express anticipation, and the Examiner's failure to demonstrate inherent anticipation, the rejection under 102(e) should be withdrawn.

---

[19] *RCA Corp. v. applied Digital Data Sys., Inc.*, 730 F.2d 1440, 221 USPQ 385, 388 (Fed. Cir. 1984).

[20] (Emphasis added) MPEP § 2112, citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990); see also *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

[21] Office Action, page 7, last full sentence.

C. Applicant Need Not Provide A Rebuttal

The Examiner argued that "the burden is upon the applicant to prove that the claimed method is functionally different than that taught by the prior art and to establish patentable differences."[22] This turns the burden of proof on its head. The MPEP directs the Examiner that only when

> "a reference . . . is made the basis of a rejection *and* the Examiner presents evidence or reasoning tending to show inherency, [does] the burden shift to the applicant to show an unobvious difference."[23]

Since the Examiner has presented neither evidence nor reasoning in support of inherency, the burden never shifted to Applicant. Accordingly, Applicant need not make any showing, and is entitled to allowance of the claims in issue.

D. Inherency Is Rebutted

While Applicant need not provide a rebuttal, nonetheless, to expedite Applicant's business interests, Applicant rebuts any alleged inherency with the following arguments and evidentiary material which demonstrate that the claims' limitations do not "*necessarily* flows from the teachings of the applied prior art."[24]

1. Superfibronectin

Pasqualini *et al.* discloses inhibiting metastases by administering superfibronectin (sFN).[25] However, this does **not necessarily** disclose the limitation of "agent that interferes with specific binding of the $\alpha 5\beta 1$ integrin to a ligand," or of "reducing or inhibiting angiogenesis" by such an agent, as recited by each of the rejected Claims 1-5, 9-13, 55-6, 68, 69, 71, 72, and 75. First, the prior art suggests alternative mechanisms for sFN action which do **not** implicate $\alpha 5\beta 1$ integrin. For example, Pasqualini *et al.* discloses that sFN "may

---

[22] Office Action, page 7, last full sentence.

[23] MPEP 2112.

[24] MPEP § 2112, citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990); see also *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

[25] Pasqualini *et al.*, Figure 8; and column 3, lines 23-28..

ameliorate . . . angiogenesis."[26] However, this disclosure does not amount to an inherent teaching of the claims' limitations. In particular, it is important to note that the α5β1 integrin is only one of several receptors to which fibronectin binds. Specifically, fibronectin is known to bind with several other receptors such as α3β1,[27] α4β1,[28] αvβ1,[29] α4β7,[30] αvβ3[31], which are expressed on endothelial cells and which have proven or potential roles in angiogenesis. Thus, when Pasqualini *et al.* suggests that sFN may inhibit angiogenesis, it is probable that this inhibition may result from sFN's interference with the binding of any one or more of the α3β1, α4β1, α5β1, αvβ1, α4β7, αvβ3 receptors to their respective ligands. Since not one, but several **alternative** mechanisms exist for Pasqualini *et al.*'s postulated anti-angiogenic action of sFN, it follows that sFN does **not necessarily** "interfere with specific binding of the α5β1 integrin to a ligand," as recited by each of the rejected claims. This precludes inherency.

Second, Pasqualini *et al.* itself expressly teaches that sFN acts through pathways which do not implicate α5β1 integrin. Importantly, Pasqualini *et al.* discloses that:

---

[26] Pasqualini *et al.*, column 3, lines 63-67.

[27] Takada *et al.* (1988) "Extracellular matrix receptors, ECMRII and ECMRI, for collagen and fibronectin correspond to VLA-2 and VLA-3 in the VLA family of heterodimers." J. Cell. Biochem.37(4):385-93; Takada *et al.* (1987) "Fibronectin receptor structures in the VLA family of heterodimers." Nature 326(6113):607-9; and Elices *et al.* (1991) "Receptor functions for the integrin VLA-3: fibronectin, collagen, and laminin binding are differentially influenced by Arg-Gly-Asp peptide and by divalent cations." J. Cell Biol. 112(1):169-81; attached as Tab 1.

[28] Masumoto & Hemler (1993) "Multiple activation states of VLA-4. Mechanistic differences between adhesion to CS1/fibronectin and to vascular cell adhesion molecule-1." J. Biol. Chem. 268(1):228-34; attached as Tab 2.

[29] Zhang *et al.* "The alpha v beta 1 integrin functions as a fibronectin receptor but does not support fibronectin matrix assembly and cell migration on fibronectin." Journal of Cell Biology, 1993 Jul, 122(1):235-42; attached as Tab 3.

[30] Ruegg, et. al. (1992) "Role of integrin alpha 4 beta 7/alpha 4 beta P in lymphocyte adherence to fibronectin and VCAM-1 and in homotypic cell clustering," J. Cell Biol. 117(1):179-189; attached as Tab 4.

[31] Orlando R and Cheresh D (1991) "Arginine-Glycine-Aspartic Acid binding leading to molecular stabilization between Integrin avb3 and its ligand" J. Biol. Chem. 266:19543-19550; attached as Tab 5.

> "Whereas cells attach to fibronectin through integrin, cell attachment to sFN is mediated by both *integrins and other distinct receptors*."[32]

In other words, since the actions of sFN may be mediated by several receptors other than the recited α5β1 integrin receptor, then Pasqualini *et al.*'s observed inhibition of angiogenesis **cannot necessarily** be the result of only the recited interference with the α5β1 integrin.

Third, Pasqualini *et al.*'s data demonstrates **directly opposite** biological effects when administering sFN, as compared to the biological effects which were observed by the inventor of the instant application when using an agent that interferes with the specific binding of the α5β1 integrin to a ligand. Specifically, Pasqualini *et al.* discloses that sFN **inhibits** cell migration on collagen.[33] In contrast, the instant specification discloses that inhibiting the specific α5β1 integrin binding to a ligand "did **not affect** endothelial cell migration on . . . collagen."[34] Because Pasqualini *et al.*'s administration of sFN yields a conflicting biological effect when compared to the instant specification's disclosed administration of an agent that interferes with the specific binding of the α5β1 integrin to a ligand, this **refutes** any improper inference that Pasqualini *et al.*'s administration of sFN **necessarily** results in the recited interference with the specific binding of α5β1 integrin binding to a ligand.

Because Pasqualini *et al.*'s inhibition of metastasis by administering sFN does **not** expressly or inherently disclose the limitation of "agent that interferes with specific binding of the α5β1 integrin to a ligand," it follows that this reference also must fail to disclose the limitation of "reducing or inhibiting angiogenesis" by such an agent, as recited by each of the rejected Claims 1-5, 9-13, 55-6, 68, 69, 71, 72, and 75. This precludes anticipation of each of the rejected claims.

As to the rejected Claim 3 which recites an "agent that interferes with specific binding of the α5β1 integrin to fibronectin," inherency does not exist as to this additional limitation. Fibronectin is only one of several ligands which bind to α5β1 integrin. In particular, α5β1

---

[32] (Emphasis added) Pasqualini *et al.*, column 1, lines 60-63.

[33] Pasqualini *et al.*, Figure 7; column 12, lines 37-44; and column 25, lines 9-14.

[34] Specification, page 45, lines 9-16.

integrin binds to fibrinogen,[35] the immunoglobulin superfamily molecule L1,[36] endostatin (a fragment of collagen XVIII),[37] Angiopoietin 1,[38] EMF 10 (snake venom protein),[39] and echistatin[40] (another snake venom protein). In view of this, Claim 3's recitation of "reducing or inhibiting angiogenesis" may be caused by an agent which interferes with the specific binding of $\alpha 5\beta 1$ integrin to fibrinogen, molecule L1, endostatin, Angiopoietin 1, EMF 10, and/or echistatin, and **not necessarily** by the agent's interference with the specific binding of $\alpha 5\beta 1$ integrin to its fibronectin ligand.[41] In other words, the inhibition of the specific binding of $\alpha 5\beta 1$ integrin to fibronectin is **not the only** mechanisms for "reducing or inhibiting angiogenesis" as recited by the instantly claimed methods. In view of the alternative pathways for inhibiting angiogenesis, it **cannot** be concluded that Pasqualini *et al.*'s sFN-

---

[35] Suehiro, et.al. (1997) "Fibrinogen is a Ligand for Integrin a5b1 on Endothelial cells" Journal of Biological Chemistry 272 5360-5366; Suehiro *et al.*, (2000) "Fibrinogen binds to integrin alpha(5)beta(1) via the carboxyl-terminal RGD site of the Alpha-chain." Journal of Biochemistry 2000 Oct, 128(4):705-10; attached as Tab 6.

[36] Felding Haberman, et. al. (1997) "A single immunoglobulin-like domain of the human neural cell adhesion molecule L1 supports adhesion by multiple vascular and platelet integrins." Journal of Cell Biology 139:1567-81; Silletti *et al.* (2000) "Plasmin sensitive dibasic sequences in the third fibronectin-like domain of L-cell adhesion molecule (CAM) facilitate homomultimerization and concomitant integrin recruitment." Journal of Cell Biology 149:1485-502; attached as Tab 7.

[37] Rehn *et al.* (2001) "Interaction of endostatin with integrins implicated in angiogenesis" PNAS 98:1024-1029; attached at Tab 8.

[38] Carlson *et al.* (2001) "Direct cell adhesion to the angiopoietins mediated by integrins," J. Biol Chem. 276:26516-26525; attached at Tab 9.

[39] Marcinkiewicz *et al.*(1999) "Structural and functional characterization of EMF10, a heterodimeric disintegrin from Eristocophis macmahoni venom that selectively inhibits a5b1 integrin" Biochemistry 38:13302-13309; attached at Tab 10.

[40] Wierzbicka-Potynowski et al. (1999) "Structural requirements of echistatin for the recognition of alpha(v)beta(3) and alpha(5)beta(1) integrins," J. Biol. Chem. 274(53):37809-14; attached at Tab 11.

[41] Applicant's argument is made without intending to limit the invention to any particular mechanisms, while recognizing that an understanding of the mechanism is not necessary to patentability. Rather it is made to illustrate the probable existence of alternative mechanisms of action for the instantly claimed methods.

mediated inhibition of angiogenesis must **necessarily** be the result only of interference with specific binding of the α5β1 integrin to fibronectin. For this additional reason, Claim 3's method cannot be inherent in Pasqualini *et al.*'s method.

2. Peptides

Pasqualini *et al.* further discloses inhibiting metastases by administering "the RGD-containing peptides GRGDSP (SEQ ID NO:16), ACDCRGDCFCG (SEQ ID NO:17 and CRRETWAC (SEQ ID NO:18)."[42] It is notable that this disclosure by Pasqualini *et al.* does **not** expressly disclose that administering the RGD-containing peptides results in "reducing or inhibiting **angiogenesis**," which is recited by each of the rejected Claims 1-5, 9-13, 55-6, 68, 69, 71, 72, and 75. Rather, this disclosure relates to inhibiting **metastases**. Thus, express anticipation by this disclosure is absent.

Moreover, any alleged inherency of "reducing or inhibiting angiogenesis" is rebutted by the prior art's disclosure of alternative mechanisms (*i.e.*, other than reducing or inhibiting angiogenesis) for the mode of action of Pasqualini *et al.*'s peptides. For example, Ruoslahti *et al.* (which was cited by the Examiner in connection with another rejection), discloses that administering peptides[43] which inhibit binding to α5β1 is associated with inhibiting the **attachment** of **tumor cells**[44] to fibronectin.[45] In other words, Ruoslahti *et al.*'s and Pasqualini *et al.*'s peptides function by an entirely different mechanisms (*i.e.*, inhibiting **cell attachment** rather than reducing **angiogenesis**) and on an entirely different target cell (*i.e.*, **tumor** cells as compared **endothelial** cells) from peptides used in the instantly claimed methods. Because an **alternative** mechanism which is other than the recited "reducing or

---

[42] Pasqualini *et al.*, Figure 8; column 3, lines 23-28; Example IX beginning on column 26, line 62.

[43] The disclosed peptides were RRETAWA (SEQ ID NO:8) and CRRETAWAC (SEQ ID NO:18). Ruoslahti *et al.*, page 31, third paragraph; and column 39 showing the sequence listing.

[44] The tumor cells used were the B2/α27 cells, C8161 cells, MG-63 cells, and WI-38 cells, "which all express α5β1." Ruoslahti *et al.*, paragraph bridging pages 31 and 32.

[45] Ruoslahti *et al.*, Figures 5 and 11; page 5, lines 24-25; page 6, fifth paragraph; page 31, lines 11-34; and page 32, lines 1-8.

inhibiting angiogenesis" exists for Pasqualini *et al.*'s observation of inhibiting metastases by administering peptides, it follows that "reducing or inhibiting angiogenesis" does **not necessarily** flow from Pasqualini *et al.*'s disclosure. This precludes inherency of the claimed invention in Pasqualini *et al.*'s disclosure.[46]

Furthermore, the Examiner is respectfully reminded that inherency cannot be established by arguing that the peptides of Pasqualini *et al.* **may** "reduce or inhibit angiogenesis." The law is clear that:

> "Inherency . . . may *not* be established by *probabilities or possibilities*. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient."[47]

Therefore, if the Examiner were to advance such an argument, inherency would not be established because such an analysis would rest upon the very kind of probability or possibility that the Federal Circuit has pointed out is **insufficient** to establish inherency.[48]

In view of the above arguments and evidentiary material,[49] any alleged inherency is rebutted. Accordingly, the rejection of Claims 1-5, 9-13, 55-6, 68, 69, 71, 72, and 75 under 35 U.S.C. § 102(e) over Pasqualini *et al.* should be withdrawn.

---

[46] Applicant notes that the arguments and evidence in support for the lack of inherent disclosure by Pasqualini *et al.* are equally applicable to a lack of inherent disclosure by Ruoslahti *et al.*

[47] *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981); see also, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, in banc suggestion declined (Jun 21, 1995).

[48] *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981); see also, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, in banc suggestion declined (Jun 21, 1995).

[49] The evidentiary material includes references cited by Applicant as well as statements which were made by Pasqualini *et al.* and Ruoslahti *et al.* that were cited by the Examiner.

3. **Rejection of Claims 1-5, 9-14, 19, 20, 55-72, And 75 Under 35 U.S.C. §103(a) Over Pasqualini *et al.* In View of Ruoslahti *et al.* and Thorpe**

Claims 1-5, 9-14, 19, 20, 55-72, and 75 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* (U.S. Patent No. 5,922,676) in view of Ruoslahti *et al.* (WO 95/14714) and Thorpe.[50] Applicant respectfully traverses because a *prima facie* case of obviousness is not established. Furthermore, even if a *prima facie* case is arguably made, it is rebutted by Applicant's arguments and evidentiary material.

A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to modify their teachings to yield the claimed invention, (b) discloses the elements of the claimed invention, **and** (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish **any** one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicant to withdrawal of the rejection of the claims in issue.[51] Applicant urges that the Examiner has failed to establish not one, but **all three** requirements as discussed below.

A. The Combined References Fail To Disclose All The Limitations Of The Claims

It is axiomatic for establishing a *prima facie* case of obviousness that "all the claim limitations must be taught or suggested by the prior art."[52] However, the Examiner has not established that the combined references disclose the limitation of "reducing or inhibiting angiogenesis," and the limitation of using an "agent that interferes with specific binding of the $\alpha 5\beta 1$ integrin to a ligand" as recited by each of the rejected claims.

---

[50] Office Action, page 8, item 10.

[51] See, *e.g.*, *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

[52] MPEP § 2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

1. Pasqualini *et al.* Does Not Disclose All The Claims' Limitations

With respect to each of the rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75, Applicant incorporates herein the above arguments in support of a lack of express or inherent disclosure by the primary reference of Pasqualini *et al.*

More specifically, Pasqualini *et al.*'s administration of sFN to inhibit metastases does not disclose the limitation of "reducing or inhibiting angiogenesis." As explained *supra*, the administration of sFN by Pasqualini *et al.* does not expressly or inherently implicate $\alpha5\beta1$ integrin, let alone "interfere with specific binding of the $\alpha5\beta1$ integrin to a ligand." Rather, the effects observed by Pasqualini *et al.* when administering sFN may be mediated by several receptors **other than** $\alpha5\beta1$ integrin. This is corroborated by Pasqualini *et al.*'s own data which demonstrates an opposite effect when administering sFN (*i.e.*, inhibiting cell migration on collagen), as compared to the effect when interfering with the specific binding of the $\alpha5\beta1$ integrin to a ligand (*i.e.*, no inhibition of cell migration on collagen). Because Pasqualini *et al.*'s administration of sFN does not amount to express or inherent disclosure of the limitation of "agent that interferes with specific binding of the $\alpha5\beta1$ integrin to a ligand," it follows that this reference also must fail to disclose the additional limitation of "reducing or inhibiting angiogenesis" by such an agent.

Also, Pasqualini *et al.*'s inhibition of metastasis using RGD-containing peptides neither expressly nor inherently discloses the limitation of "reducing or inhibiting angiogenesis" because these peptides may function by the alternative mechanism of inhibiting the **attachment** of **tumor cells** to fibronectin, instead of inhibiting **angiogenesis** by **endothelial cells**.

The Examiner argued that Pasqualini *et al.* teaches the CRRETAWAC peptide which is "identical to claimed SEQ ID NO:1", and that Figure 8B of Pasqualini *et al.* shows the effect of this peptide on "inhibiting melanoma *metastasis*."[53] However, as discussed *supra*, inhibiting **metastasis** is not the equivalent to either an express or inherent disclosure of "reducing or inhibiting **angiogenesis**" which is recited in each of the rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75. Nor does the Examiner provide any cogent evidence why

[53] (Emphasis added) Office Action, page 10, first full paragraph.

inhibiting angiogenesis by endothelial cells necessarily follows from inhibiting metastasis by tumor cells. Accordingly, the Examiner's argument does not establish that all the limitations of the claims are disclosed by Pasqualini *et al.*

Moreover, the Examiner admitted that Pasqualini *et al.* "does not teach the peptide is SEQ ID NO:1 (claim 14), the peptide linked to a cytotoxin (claim 19), wherein the cytotoxin is a cancer chemotherapeutic drug (claim 20), wherein the agent is administered into a neoplasm (claim [*sic.*] 58, wherein the agent is administered by eye drops (claim 70)."[54] In view of this admitted additional deficiency of Pasqualini *et al.*'s disclosure with respect to Claims 14, 19, 20, 58, and 70, Pasqualini *et al.* fails to make these claims obvious.

2. Ruoslahti *et al.* Fails To Disclose All The Claims' Limitations

The secondary reference of Ruoslahti *et al.* does not bridge the gap in Pasqualini *et al.*'s disclosure. Ruoslahti *et al.* discloses "methods useful for *inhibiting angiogenesis* . . . [which] involves administering to an individual a peptide of the invention that binds to the *αvβ3 integrin.*"[55] However, this is distinguished from the instantly recited limitations because Ruoslahti *et al.*'s inhibition of angiogenesis relates to using a peptide which binds to **αvβ3**, not to one which inhibits the specific binding of the recited **α5β1** to a ligand.

Ruoslahti *et al.* also discloses a "method useful for *inhibiting metastasis* of tumor cells expressing, for example, the α5β1 or αvβ3 integrin involving administering to an individual a peptide of this invention that binds to these integrins."[56] However, this fails to expressly disclose the limitation of "reducing or inhibiting angiogenesis" because Ruoslahti *et al.*'s disclosure concerns inhibiting **metastasis**, not reducing or inhibiting **angiogenesis**. Moreover, inherent disclosure of "reducing or inhibiting angiogenesis" is also lacking. As explained above, Ruoslahti *et al.* discloses peptides[57] which inhibit binding to α5β1, and that these

---

[54] Office Action, page 10, second full paragraph.

[55] Ruoslahti *et al.*, page 4, lines 23-27. See also, page 20, lines 22-25; Claim 64; nd Claim 65.

[56] Ruoslahti *et al.*, page 4, lines 28-32.

[57] The disclosed peptides were RRETAWA (SEQ ID NO:8) and CRRETAWAC (SEQ ID NO:18). Ruoslahti *et al.*, page 31, third paragraph; and column 39 showing the

peptide result in inhibiting the **attachment** of **tumor cells**[58] to fibronectin.[59] Since Ruoslahti *et al.* expressly discloses the existence of an **alternative** mechanism (*i.e.*, inhibiting cell attachment to a substrate) which is different from the recited "reducing or inhibiting angiogenesis," and since this mechanism impacts tumor cells rather than endothelial cells (which participate in the recited "angiogenesis"), then the limitation of "reducing or inhibiting angiogenesis" does **not necessarily** flow from Ruoslahti *et al.*'s disclosure. This negates any alleged inherency of the claimed invention in Ruoslahti *et al.*'s disclosure.

Importantly, even if the Examiner were to argue that inherency exists because the peptides of Ruoslahti *et al.* **may** "reduce or inhibit angiogenesis," such an argument must fail because:

> "Inherency . . . may *not* be established by *probabilities or possibilities*. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient."[60]

In view of the above, Ruoslahti *et al.* (like Pasqualini *et al.*) fails to expressly or inherently disclose the limitation of "reducing or inhibiting angiogenesis."

The Examiner argued that Ruoslahti *et al.* discloses using a "peptide [which] selectively binds alpha 5 beta 1 integrin" to inhibit "metastasis of tumor cells expressing alpha 5 beta 1 integrin," and that one of the peptides "specifically inhibits cell attachment to fibronectin."[61] However, as explained above, this disclosure does not amount to an express or inherent disclosure of the limitation of "reducing or inhibiting angiogenesis."

---

sequence listing.

[58] The tumor cells used were the B2/α27 cells, C8161 cells, MG-63 cells, and WI-38 cells, "which all express α5β1." Ruoslahti *et al.*, paragraph bridging pages 31 and 32.

[59] Ruoslahti *et al.*, Figures 5 and 11; page 5, lines 24-25; page 6, fifth paragraph; page 31, lines 11-34; and page 32, lines 1-8.

[60] *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981); see also, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, in banc suggestion declined (Jun 21, 1995).

[61] Office Action, paragraph bridging pages 10 and 11.

Accordingly, Ruoslahti *et al.* does not bridge the gap of Pasqualini *et al.* since both references are silent on the limitation of "reducing or inhibiting angiogenesis."

3. Thorpe Lacks All The Limitations Of The Claims

The third reference of Thorpe also fails to provide that which both Pasqualini *et al.* and Ruoslahti *et al.* omit. Thorpe discloses conjugating cytotoxins to peptides. However, this disclosure is silent on "reducing or inhibiting angiogenesis" as recited by each of the rejected claims.

From the above, Pasqualini *et al.* in combination with Ruoslahti *et al.* and Thorpe lack an express or inherent teaching of the limitation of "reducing or inhibiting angiogenesis," which is recited by each of the rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75. In view of the combined references' failure to disclose each of the limitations of the rejected claims, the first prong of a *prima facie* case of obviousness is not established. This alone necessitates withdrawal of the rejection of the claims under 35 U.S.C. §103.

B. The Combined References Do Not Provide A Motivation To Practice The Recited Combination Of Steps

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be **motivated** to modify the reference to arrive at the **claimed invention**.[62] In particular,

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the *claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed."[63]

The Examiner advanced four arguments in support of motivation to combine the references. The Examiner first argued that motivation exists with respect to each of the rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75 because it "would have been prima facie obvious to one of

---

[62] *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

[63] (Emphasis added) *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998); *Robotic Vision Systems Inc. v. View Engineering Inc.*, 51 USPQ2d 1948 (Fed. Cir. 1999).

ordinary skill in the art at the time the invention was made to substitute SEQ ID NO:1 or SEQ ID NO:12 of . . . [Ruoslahti *et al.*] for the sFN of . . . [Pasqualini *et al.*] because both agents bind to alpha 5 beta 1 integrin and because . . . [Pasqualini *et al.*] specifically teaches that SEQ ID NO 18 inhibits cancer cell metastasis in a manner *substantially equivalent to that of sFN* and . . . [Ruoslahti *et al.*] specifically teaches a method useful for inhibiting metastasis using the recited peptides."[64] However, this argument suffers from two problems.

First, the Examiner's argument improperly narrows the scope of the claims to inhibiting cancer metastasis. However, except for Claims 11 and 60, none of the rejected claims recite the limitation of inhibiting metastasis. Rather, each of the rejected claims recites "reducing or inhibiting angiogenesis," without regard to whether angiogenesis is in a cancer metastasis.

Second, contrary to Federal Circuit law, the Examiner's argument neglects to consider the elements of the "claimed invention."[65] The Examiner is respectfully reminded that the claimed invention recites the limitation of "**reducing or inhibiting angiogenesis**." However, none of the Examiner's arguments in support of a motivation to combine the references' teachings relates to this limitation. Rather, each of the Examiner's arguments refers to a motivation to **inhibit metastasis**. Metastasis is irrelevant.

Further, the Examiner has failed to provide **clear and particular evidence** to establish a nexus between inhibiting metastasis and inhibiting angiogenesis. The law requires that evidence of a suggestion, teaching, or motivation to combine prior art references:

> "must be clear and particular."[66] "Broad conclusory statements . . . standing alone, are not evidence."[67]

---

[64] Office Action, page 11, last paragraph.

[65] *In re Rouffet*, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998).

[66] *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999), *citing C.R. Bard*, 157 F.3d 1340 at 1352, 48 USPQ2d at 1232.

[67] *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999), citing *McElmurry v. Arkansas Power & Light Co.*, 995 F.2d 1576, 1578, 27 USPQ2d 1129,1131 (Fed. Cir. 1993) and *In re Sichert*, 566 F.2d 1154, 1164, 196 USPQ 209, 217 (CCPA 1977).

Indeed, the Examiner did not advance **any** evidence, much less clear and particular evidence, which supports a nexus between inhibiting metastasis, and the recited reducing or inhibiting of angiogenesis. Because the Examiner has failed properly to consider the legal standard, motivation to combine the cited references cannot be established with respect to any of the rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75.

Furthermore, any attempt by the Examiner to implicate an alleged inherency of "reducing or inhibiting angiogenesis" in the cited references must fail because inherency has **no** place in an obviousness analysis. The Federal Circuit has unequivocally stated that:

> "Inherency and obviousness are distinct concepts."[68] "[A] retrospective view of inherency is *not* a substitute for some teaching or suggestion supporting an obviousness rejection."[69] "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."[70]

Thus, any attempt by the Examiner to rely on inherency to establish motivation by the cited references is improper. Further, even if applicable (which it is not), inherency is absent as discussed *supra* for each of the Pasqualini *et al.* and Ruoslahti *et al.* references.

Indeed, the Examiner cannot advance evidence in support of a motivation for "reducing or inhibiting angiogenesis" by using the recited "agent that interferes with specific binding of the $\alpha 5\beta 1$ integrin" because the prior art **did not know** that $\alpha 5\beta 1$ integrin expression was associated with angiogenesis. Indeed, the instant specification is the **first** report of such an association. In other words, since the artisan did not even know that $\alpha 5\beta 1$ integrin expression was associated with angiogenesis, then it follows that the artisan **could not have been motivated** to reduce or inhibit angiogenesis by interfering with the specific binding of $\alpha 5\beta 1$ to a ligand, as recited in the claims.

For the above reasons, motivation to combine the cited references to arrive at the invention as claimed in each of rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75 has not been established.

---

[68] *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

[69] (Emphasis added) *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

[70] *In re Newell*, 891 F.2d 899, 901,13 USPQ2d 1248, 1250 (Fed. Cir.1989).

The Examiner's second argument was that "one of ordinary skill in the art would have been motivated to administer the agent for treatment of ocular pathology by administration of eye drops because . . . [Pasqualini *et al.*] specifically teaches the topical administration of the agent of the invention."[71] However, this disclosure is **irrelevant** to rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75 because none of these claims recites administration of the agent using eye drops.[72] Also, with respect to each of the rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75, this disclosure does not add to the **deficient motivation** for reducing or inhibiting angiogenesis, for the same reasons which were discussed *supra* in connection with the Examiner's first argument.

The Examiner's third argument was that "one of ordinary skill in the art would have been motivated to produce the claimed cytotoxin-linked agents in view of the teachings that such cytotoxin-linked agents are useful for diagnosis of refractory tumors and the general knowledge that antibodies can be successfully targeted to tumor cells."[73] However, this argument is **irrelevant** to rejected Claims 1-5, 9-14, 55-72, and 75 because none of these claims recites cytotoxin-linked agents.[74] Also, with respect to each of the rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75, this argument adds nothing to the **inadequate motivation** for reducing or inhibiting angiogenesis, as explained above in relation to the Examiner's first argument.

The Examiner's fourth argument was that "one of ordinary skill in the art would have been motivated to inject the agents directly into the tumor in the methods of either . . . [Pasqualini *et al.* or Ruoslahti *et al.*] in order to reduce diffusion and non-specific sequestration of the agent."[75] Nonetheless, this argument is **irrelevant** to any of the rejected Claims 1-5, 9-14, 19, 20, 55-66, 68-72, and 75, because none of these claims recites injecting

---

[71] Office Action, page 12, first full paragraph.

[72] Only rejected Claim 70 recites administration of eye drops.

[73] Office Action, page 12, second full paragraph.

[74] Only rejected Claims 19 and 20 recite an agent linked to a cytotoxin.

[75] Office Action, page 12, second full paragraph.

the agent.[76] Also, with respect to each of the rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75, this argument fails to supplement the **insufficient motivation** for reducing or inhibiting angiogenesis, as explained above in connection with the Examiner's first argument.

In view of the above, a motivation to combine the teachings of the references to arrive at the claimed invention is lacking. Accordingly, a *prima facie* case of obviousness must fail.

C. A Reasonable Expectation Of Success Is Not Established

A fundamental requisite of establishing a *prima facie* case of obviousness is that there is a reasonable expectation of success in practicing the recited method steps.

> "[T]he reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure."[77]

It is notable that the Examiner has **not** advanced a single argument or shred of evidence to establish that one skilled in the art would have had a reasonable expectation of success in reducing or inhibiting angiogenesis by using an agent which inhibits the specific binding of $\alpha 5\beta 1$ integrin to a ligand. This omission negates a *prima facie* case of obviousness, and entitles Applicant to allowance of the claims in issue.

Moreover, any attempted inference of a reasonable expectation of success which is based on the cited references must fail. This is because the prior art in general, and the cited references in particular, were **ignorant** of a role for $\alpha 5\beta 1$ integrin in angiogenesis; this role was first discovered and disclosed by Applicant in the instant specification. In view of the prior art's ignorance, and since the reasonable expectation of success must be founded in the prior art, not Applicant's disclosure, it cannot be argued that the cited references would have taught a reasonable expectation of success in inhibiting angiogenesis by using an agent which inhibits the specific binding of $\alpha 5\beta 1$ integrin to a ligand.

Nor can the Examiner rely on alleged inherency to establish a reasonable expectation of success in practicing the recited steps; as explained above:

---

[76] Only rejected Claim 67 recites administering an agent into neoplasm. However, such administering is not limited to injecting into a neoplasm.

[77] *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) as cited in *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

> "Inherency and obviousness are distinct concepts."[78] "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."[79]

Thus, any attempt by the Examiner to rely on inherency in support of obviousness must fail because inherency is inapplicable in an obviousness analysis. Furthermore, as discussed above, inherency is lacking anyway as discussed *supra* for each of the Pasqualini *et al.* and Ruoslahti *et al.* references.

Because, not one, but each of the **three** elements of a *prima facie* case of obviousness remains lacking, a *prima facie* case of obviousness cannot be established. It is therefore respectfully requested that the rejection of Claims 1-5, 9-14, 19, 20, 55-72, and 75 under 35 U.S.C. § 103(a) for alleged obviousness be withdrawn.

CONCLUSION

All grounds of rejection and objection of the Office Action of March 9, 2001 having been addressed, reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (415) 904-6500.

Dated: September 5, 2001

Kamrin T. MacKnight
Registration No. 38,230

Please direct all communication to:

Kamrin MacKnight
MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
415.904.6500

---

[78] *W.L. Gore & Assoc., Inc v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984), citing *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

[79] *In re Newell*, 891 F.2d 899, 901,13 USPQ2d 1248, 1250 (Fed. Cir.1989).

APPENDIX I
MARKED-UP VERSION OF SPECIFICATION'S REPLACEMENT PARAGRAPHS AND REWRITTEN, ADDED, AND/OR CANCELLED CLAIMS

The following is a marked-up version of the specification's replacement paragraphs pursuant to 37 C.F.R. §1.121(b), as well as a marked-up version of the claims pursuant to 37 C.F.R. §1.121 (c)(1)(ii) with instructions and markings showing changes made herein to the previous version of record of the specification and claims. Underlining denotes added text while bracketing denotes deleted text.

IN THE SPECIFICATION

On page 1, line 4, please change "06/084,850" to --60/084,850--.

IN THE CLAIMS

Cancel Claims 6-8, 15-18, 21-54, 73, 74, and 76-79.

Add the following new Claims 80-120:

80. (New) The method of Claim 1, wherein the binding of said agent to said $\alpha 5\beta 1$ integrin is at least two-fold greater than the binding of said agent to an integrin other than $\alpha 5\beta 1$ integrin.

81. (New) The method of Claim 80, wherein said integrin other than $\alpha 5\beta 1$ integrin is $\alpha V\beta 3$ integrin.

82. (New) The method of Claim 1, wherein the binding of said agent to said $\alpha 5\beta 1$ integrin is at least five-fold greater than the binding of said agent to an integrin other than $\alpha 5\beta 1$ integrin.

83. (New) The method of Claim 82, wherein said integrin other than $\alpha 5\beta 1$ integrin is $\alpha V\beta 3$ integrin.

84. (New) The method of Claim 1, wherein the binding of said agent to said $\alpha 5\beta 1$ integrin is at least ten-fold greater than the binding of said agent to an integrin other than $\alpha 5\beta 1$ integrin.

85. (New) The method of Claim 84, wherein said integrin other than $\alpha 5\beta 1$ integrin is $\alpha V\beta 3$ integrin.

86. (New) The method of Claim 1, wherein said agent does not interfere with the specific binding of a ligand to an integrin other than $\alpha 5\beta 1$ integrin.

87. (New) The method of Claim 1, wherein said tissue is in a human subject.

88. (New) The method of Claim 10, wherein said malignant neoplasm is selected from the group consisting of a sarcoma, a mesothelioma, a teratocarcinoma, an astrocytoma, and a glioblastoma.

89. (New) The method of Claim 12, wherein said carcinoma is selected from the group consisting of a breast carcinoma, a colon carcinoma, an ovarian carcinoma and a pancreatic carcinoma.

90. (New) The method of Claim 55, wherein the binding of said agent to said $\alpha 5\beta 1$ integrin is at least two-fold greater than the binding of said agent to an integrin other than $\alpha 5\beta 1$ integrin.

91. (New) The method of Claim 90, wherein said integrin other than $\alpha 5\beta 1$ integrin is $\alpha V\beta 3$ integrin.

92. (New) The method of Claim 55, wherein the binding of said agent to said $\alpha 5\beta 1$ integrin is at least five-fold greater than the binding of said agent to an integrin other than $\alpha 5\beta 1$ integrin.

93. (New) The method of Claim 92, wherein said integrin other than $\alpha 5\beta 1$ integrin is $\alpha V\beta 3$ integrin.

94. (New) The method of Claim 55, wherein the binding of said agent to said $\alpha 5\beta 1$ integrin is at least ten-fold greater than the binding of said agent to an integrin other than $\alpha 5\beta 1$ integrin.

95. (New) The method of Claim 94, wherein said integrin other than $\alpha 5\beta 1$ integrin is $\alpha V\beta 3$ integrin.

96. (New) The method of Claim 55, wherein said agent does not interfere with the specific binding of a ligand to an integrin other than $\alpha 5\beta 1$ integrin.

97. (New) The method of Claim 55, wherein said ligand is fibronectin.

98. (New) The method of Claim 55, wherein said tissue comprises ocular tissue.

99. (New) The method of Claim 98, wherein said ocular tissue is selected from the group consisting of retina, macula and cornea.

100. (New) The method of Claim 55, wherein said tissue comprises a neoplasm.

101. (New) The method of Claim 100, wherein said neoplasm is a malignant neoplasm.

102. (New) The method of Claim 101, wherein said malignant neoplasm is selected from the group consisting of a sarcoma, a mesothelioma, a teratocarcinoma, an astrocytoma, and a glioblastoma.

103. (New) The method of Claim 101, wherein said malignant neoplasm is a metastatic malignant neoplasm.

104. (New) The method of Claim 101, wherein said malignant neoplasm is a carcinoma.

105. (New) The method of Claim 104, wherein said carcinoma is selected from the group consisting of a breast carcinoma, a colon carcinoma, an ovarian carcinoma and a pancreatic carcinoma.

106. (New) The method of Claim 55, wherein said agent comprises a peptide.

107. (New) The method of Claim 106, wherein said peptide comprises the amino acid sequence CRRETAWAC (SEQ ID NO: 1).

108. (New) The method of Claim 55, wherein said agent is linked to a cytotoxin.

109. (New) The method of Claim 108, wherein said cytotoxin is a cancer chemotherapeutic drug.

110. (New) The method of Claim 57, wherein the binding of said agent to said $\alpha 5\beta 1$ integrin is at least two-fold greater than the binding of said agent to an integrin other than $\alpha 5\beta 1$ integrin.

111. (New) The method of Claim 110, wherein said integrin other than $\alpha 5\beta 1$ integrin is $\alpha V\beta 3$ integrin.

112. (New) The method of Claim 57, wherein the binding of said agent to said $\alpha 5\beta 1$ integrin is at least five-fold greater than the binding of said agent to an integrin other than $\alpha 5\beta 1$ integrin.

113. (New) The method of Claim 112, wherein said integrin other than $\alpha 5\beta 1$ integrin is $\alpha V\beta 3$ integrin.

114. (New) The method of Claim 57, wherein the binding of said agent to said $\alpha 5\beta 1$ integrin is at least ten-fold greater than the binding of said agent to an integrin other than $\alpha 5\beta 1$ integrin.

115. (New) The method of Claim 114, wherein said integrin other than $\alpha 5\beta 1$ integrin is $\alpha V\beta 3$ integrin.

116. (New) The method of Claim 57, wherein said agent does not interfere with the specific binding of a ligand to an integrin other than $\alpha 5\beta 1$ integrin.

117. (New) The method of Claim 57, wherein said agent comprises a peptide.

118. (New) The method of Claim 117, wherein said peptide comprises the amino acid sequence CRRETAWAC (SEQ ID NO: 1).

119. (New) The method of Claim 57, wherein said agent is linked to a cytotoxin.

120. (New) The method of Claim 119, wherein said cytotoxin is a cancer chemotherapeutic drug.

IN THE ABSTRACT

ABSTRACT[OF THE INVENTION

METHODS FOR DETECTING AND INHIBITING ANGIOGENESIS]

The present invention provides methods for reducing or inhibiting angiogenesis in a tissue, by contacting α5β1 integrin in the tissue with an agent that interferes with specific binding of the α5β1 integrin to a ligand [expressed in the tissue]; and methods of identifying angiogenesis in a tissue, by contacting the tissue with an agent that specifically binds α5β1 integrin, and detecting specific binding [of the agent to α5β1 integrin associated with a blood vessel in the tissue]. Also provided are methods of diagnosing a pathological condition characterized by angiogenesis [in a tissue in an individual]. The invention [further] provides methods of reducing or inhibiting angiogenesis [in a tissue in an individual,] by administering to the individual an agent that interferes with the specific binding of α5β1 integrin to a ligand [expressed in the tissue]; and methods of reducing [the severity of] a pathological condition associated with angiogenesis in an individual, by administering to the individual an agent that interferes with specific binding of α5β1 integrin to a ligand [in a tissue associated with the pathological condition]. The invention also provides methods of identifying an agent that reduces or inhibits angiogenesis associated with α5β1 integrin expression [in a tissue by contacting a tissue exhibiting angiogenesis associated with α5β1 integrin expression with an agent, and detecting a reduction or inhibition of angiogenesis in the tissue].